WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH095 trade name]† 100 micrograms/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution contains 100 micrograms carbetocin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A clear, colourless, sterile solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH095 trade name] is indicated for the prevention of postpartum haemorrhage due to uterine atony.

4.2 Posology and method of administration

Posology

[RH095 trade name] must be administered as soon as possible after delivery of the infant and preferably before delivery of the placenta. It should be administered in an obstetric unit by appropriately skilled and trained health care providers.

Caesarean section under epidural or spinal anaesthesia

A single dose of 100 micrograms carbetocin (1 mL [RH095 trade name]) by slow intravenous injection (over 1 minute) after delivery of the infant.

There are limited data on the use of carbetocin with general anaesthesia.

Vaginal delivery

A single dose of 100 micrograms carbetocin (1 mL [RH095 trade name]) by slow intravenous injection (over 1 minute) or by intramuscular injection, after delivery of the infant.

Children and adolescents

Only limited data are available on the safety and efficacy of carbetocin in adolescents after the menarche (see "Pharmacological properties"). In adolescents from the age of 15 years, the same dose as in adults may be administered under adequate supervision, if indicated.

[RH095 trade name] is not recommended in adolescents under 15 years of age, i.e. those who are not yet fully mature, due to lack of data.

There is no indication for use in pre-pubescent children.

Elderly

There is no indication for use in post-menopausal women.

Hepatic or renal impairment

The pharmacokinetics of carbetocin in patients with hepatic or renal impairment have not been investigated. Therefore, [RH095 trade name] should not be used in these patients (see "Contraindications").

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Method of administration

For intravenous or intramuscular administration.

For intravenous administration [RH095 trade name] must be administered slowly, over 1 minute.

[RH095 trade name] is for single administration only. No further doses of carbetocin should be administered.

4.3 Contraindications

[RH095 trade name] is contraindicated in the following circumstances:

- Pregnancy and labour before delivery of the infant
- For induction or augmentation of labour
- Serious cardiovascular disorders
- Epilepsy
- Renal or hepatic disorders
- Hypersensitivity to carbetocin, oxytocin or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

[RH095 trade name] should be used only in obstetric units by appropriately skilled and trained health care providers.

Persistent or excessive bleeding

If uterine bleeding persists, the cause must be determined. Possible causes are retained placental fragments, injuries to the perineum, vagina or cervix, inadequate emptying or repair of the uterus after caesarean section, or disorders of blood coagulation.

If uterine hypotonia or atony persists after administration of [RH095 trade name], with consequent excessive bleeding, therapy with another uterotonic can be considered. There are no data on additional doses of carbetocin or on the use of carbetocin following persistent uterine atony after oxytocin administration.

Water retention

Animal studies show that carbetocin has some antidiuretic activity (vasopressin activity: < 0.025 IU/vial) and there is, therefore, a risk of water intoxication with hyponatraemia, especially in patients receiving large volumes of infusion solutions. Attention should be paid to the early signs of water intoxication or hyponatraemia – such as drowsiness, listlessness and headache – to prevent complications such as convulsions and coma.

In the presence of migraine, asthma, cardiovascular disease, and other conditions in which a rapid increase in extracellular water may be hazardous for an already overburdened system, carbetocin should only be used after carefully weighing up of the benefits and risks and under appropriate supervision.

Cardiac risks (including QT prolongation)

Adverse cardiac effects such as bradycardia, QT prolongation, arrhythmias, and myocardial ischaemia have occurred with oxytocin, especially after rapid intravenous injection. It is not known if these effects are caused by oxytocin treatment or were caused by other simultaneously administered medicines. There are no data on a possible pathophysiological mechanism. Because carbetocin is structurally closely related to oxytocin, carbetocin should be used with special caution in patients with long-QT syndrome or other risk factors for QT prolongation (such as co-medication with drugs with a risk of QT-prolongation).

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per 100-microgram ampoule, that is to say it is essentially ‘sodium-free’.

Further precautions

[RH095 trade name] has not been investigated in patients with eclampsia. It should therefore be used with special caution in cases of eclampsia or pre-eclampsia, and patients should be carefully monitored.

Only limited data are available on the use of carbetocin in patients with (gestational) diabetes.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been undertaken with carbetocin.

There is a risk of a cumulative effect with the use of methylergometrine or oxytocin after the administration of carbetocin.

During clinical trials, [RH095 trade name] has been administered with analgesics, antibiotics, antiretrovirals, spasmolytics and agents used for epidural or spinal anaesthesia. No drug interactions were observed.

The following interactions have occurred involving oxytocin. Since carbetocin is structurally related to oxytocin, they might also occur with carbetocin:

- Prostaglandins potentiate the effect of oxytocin. Therefore, prostaglandins should not be used at the same time as carbetocin. If simultaneous use cannot be avoided, then the patient must be closely monitored.
- Inhalation anaesthetics, e.g. halothane, can potentiate the hypotensive effect and reduce the effect of carbetocin on the uterus. In case of concomitant use of such anaesthetics with oxytocin, arrhythmias have also been reported.
- Hypertension has been reported when oxytocin was given 3 to 4 hours after a vasoconstrictor was administered in conjunction with caudal-block anaesthesia.

Carbetocin can potentiate the hypertensive effect of ergot-alkaloids such as methylergometrine.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

[RH095 trade name] is contraindicated during pregnancy; it must not be used for the induction of labour (see section 4.3).

Breastfeeding

No relevant effects on milk let down have been reported during clinical trials.

Small amounts of carbetocin have been detected in breast milk of nursing women (see section 5.2 “Pharmacokinetic properties”). The small amounts of carbetocin transferred into colostrum or breast milk after a single injection of [RH095 trade name], and subsequently ingested by the infant, are likely to be degraded by enzymes in the gastrointestinal tract and therefore have probably no clinically relevant effects in the breastfed infant. Breast-feeding can be started without restrictions after the use of carbetocin.

4.7 Effects on ability to drive and use machines

No studies of the effect on the ability to respond, to drive and to use machines have been conducted. However, carbetocin can have undesirable effects such as dizziness that could impair the ability to drive.

4.8 Undesirable effects

The following statements are based on clinical trials in which carbetocin was used in the context of a Caesarean section. However, a similar safety profile is to be expected on use after vaginal delivery. The undesirable effects observed with carbetocin during clinical trials after vaginal delivery or Caesarean section were also comparable in frequency and severity to those of oxytocin.

Tabulated summary of adverse reactions

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000) or very rare (less than 1 in 10 000).

Blood and lymphatic system disorders

Common	anaemia

Immune system disorders

Not known	hypersensitivity reactions (including anaphylactic reactions)

Nervous system disorders

Very common	headache, tremor
Common	dizziness

Cardiac disorders

Uncommon	tachycardia (see also section 4.4)

Vascular disorders

Very common	hypotension, flushing

Respiratory, thoracic and mediastinal disorders

Common	dyspnoea

Gastrointestinal disorders

Very common	nausea, abdominal pain
Common	metallic taste, vomiting

Skin and subcutaneous tissue disorders

Very common	pruritus

Musculoskeletal and connective tissue disorders

Common	back pain

General disorders and administration site conditions

Very common	feeling of warmth
Common	chills, pain, chest pain, sweating

Reactions at the administration site were not specifically investigated. As with other drugs, local irritation is likely, especially with intramuscular administration.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder (SafetyMailboxCarbetocin@Ferring.com) or, if available, via the national reporting system.

4.9 Overdose

An overdose with uterotonic agents such as carbetocin can induce uterine hyperactivity. Symptoms of an overdose observed with oxytocin are also likely with carbetocin. If carbetocin is used before delivery of the infant (see "Contraindications"), hyperstimulation of the uterus with strong (hypertonic) or prolonged (tetanic) contractions can occur, with the risk of uterine rupture or increased postpartum haemorrhage.

An overdose may lead to hyponatraemia and water intoxication in severe cases, especially when associated with excessive concomitant fluid administration.

Treatment of overdosage consists of symptomatic and supportive therapy. If signs and symptoms of overdosage occur, oxygen should be given. In the case of water intoxication it is important to restrict fluid intake, initiate diuresis, correct electrolyte disturbances, and control convulsions if they occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oxytocin and analogues.

ATC code: H01BB03

Mechanism of action

The pharmacological and clinical properties of carbetocin are those of a long-acting oxytocin agonist.

Like oxytocin, carbetocin selectively binds to oxytocin receptors in the smooth muscle of the uterus. It thereby increases uterine tone, stimulates rhythmic contractions of the uterus and increases the frequency of existing contractions.

On the postpartum uterus, carbetocin can increase the frequency and force of spontaneous uterine contractions. The onset of uterine contractions following carbetocin is rapid after intravenous or intramuscular injection, with a first firm contraction occurring within 2 minutes.

A single 100-microgram intravenous or intramuscular dose of [RH095 trade name] administered after the delivery of the infant is sufficient to maintain adequate uterine contraction. This can reduce the risk of uterine atony and excessive bleeding.

Clinical efficacy

Prevention of uterine haemorrhage due to postpartum uterine atony following caesarean section

The efficacy of carbetocin was compared with oxytocin in a randomised, double-blind, double dummy study in 659 patients. Healthy pregnant women in whom an elective caesarean section had been performed under epidural anaesthesia were enrolled and received either 100 micrograms carbetocin as by intravenous injection or 25 IU oxytocin as an infusion over 8 hours. The proportion of patients who required an additional dose of oxytocin was 5% in the carbetocin group compared with 10% in the oxytocin group ($p = 0.031$).

Prevention of uterine haemorrhage due to postpartum uterine atony following vaginal delivery

The efficacy of carbetocin compared with oxytocin was investigated in a randomised, double-blind trial in 29,645 patients. In addition to healthy pregnant women, patients with (gestational) diabetes or pre-eclampsia, as well as those with mild or moderate hepatic or renal impairment were included. Patients with risk factors for uterine atony (such as a history of postpartum haemorrhage, macrosomia or the use of uterotonics for induction or augmentation of labour), were also enrolled. Patients were given a single intramuscular dose of either carbetocin 100 micrograms or oxytocin 10 IU. Primary endpoints were 1) the proportion of patients with a blood loss of ≥ 500 mL or given additional uterotonics, 2) the proportion of patients with a blood loss of ≥ 1000 mL.

Non-inferiority of carbetocin could be demonstrated for the first of the two co-primary endpoints. The proportion of patients with a blood loss of ≥ 500 mL and/or given additional uterotonics was 14.37% on carbetocin and 14.29% on oxytocin (relative risk [RR] 1.01; 95% CL: 0.96 to 1.06). In the second of the co-primary endpoints, non-inferiority was not achieved. A blood loss of ≥ 1000 mL occurred in 1.52% of patients on carbetocin and in 1.44% on oxytocin (RR 1.05; 95% CL 0.88 to 1.27).

Paediatric population

In the pivotal study after vaginal delivery, 151 adolescents aged 12–18 years received carbetocin at the recommended dosage of 100 micrograms; 162 adolescents were treated with oxytocin. The proportion of patients with a blood loss of ≥ 500 mL and/or given additional uterotonics (first co-primary endpoint) was 18.67% on carbetocin and 15.43% on oxytocin.

5.2 Pharmacokinetic properties

Pharmacokinetic data for [RH095 trade name] are provided in the table below. [RH095 trade name] is regarded as the same as the WHO-accepted comparator product Pabal® 100 micrograms/mL solution for injection (Ferring Pharmaceuticals Ltd) in qualitative terms and with respect to the ratio of active and other ingredients.

Pharmacokinetics of carbetocin

Absorption	
Bioavailability	77% (intramuscular administration; absolute bioavailability)
T_{max}	30 minutes (intramuscular administration)
Distribution	
Volume of distribution (mean)	22 L
Plasma protein binding *in vitro*	NA*
Tissue distribution	Small amounts are transferred into human breast milk
Metabolism	
	Carbetocin is degraded via endogenous peptidases, with an important contribution from peptidases present in the kidney.
Active metabolite(s)	Carbetocin has two metabolites with antagonistic action at the oxytocin receptor
Elimination	
Elimination half life	Approximately 33 minutes (intravenous administration) Approximately 55 minutes (intramuscular injection)
% dose excreted in urine	< 1% of dose excreted unchanged
% dose excreted in faeces	NA*
Pharmacokinetic linearity	
	Linear pharmacokinetics in the dose range of 400 µg to 800 µg

*NA: not available.

Special populations

Paediatric

No pharmacokinetic studies have been completed with children and adolescents less than 18 years old.

Renal and hepatic impairment

There are no data from patients with renal or hepatic impairment.

5.3 Preclinical safety data

In a reproductive toxicity study in rats with daily injection from parturition until day 21 of lactation, the only finding was reduced weight gain of the offspring in all groups compared to the controls. The indication did not warrant studies on fertility or embryotoxicity.

Carcinogenicity studies have not been performed with carbetocin due to the single dose nature of the indication.

The product was not mutagenic in in-vitro and in-vivo tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Methionine

Succinic acid

Mannitol

Sodium hydroxide for pH adjustment

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

Once the ampoule has been opened, the product must be used immediately. Unused solution must be discarded.

[RH095 trade name] should only be used up to the expiry date «EXP» on the pack.

6.4 Special precautions for storage

Do not store above 30°C. Keep ampoules in the outer carton, in order to protect from light.

Do not freeze.

6.5 Nature and contents of container

1 mL one-point-cut (OPC) clear, colourless Type I glass ampoule with a white OPC dot.

Pack size: 10 ampoules per carton.

6.6 Special precautions for disposal and other handling

Only clear solutions practically free from particles should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Ferring International Center SA
Chemin de la Vergognausaz 50
1162 St Prex
Switzerland

For Nigeria:
IDA Foundation Nigeria

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH095

9. DATE OF PREQUALIFICATION

4 July 2022

10. DATE OF REVISION OF THE TEXT

November 2022

References

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Carbetocin Ferring Solution for Injection 100 mcg/ml SmPC approved Jan 2022 by Swissmedic

Australian Product Information Duratocin (carbetocin) injection. Ferring: August 23, 2018 https://www.tga.gov.au/sites/default/files/auspar-carbetocin-180823-pi.pdf [Accessed November 2021]

Widmer M, Piaggio TMH, *et al.* Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth. *N Engl J Med* 2018;**379:**743-52. https://www.nejm.org/doi/full/10.1056/NEJMoa1805489 [Accessed November 2021]

Gallos ID, Papadoulou A, *et al.* Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database of Systematic Reviews 2018. https://doi.org/10.1002/14651858.CD011689.pub3 [Accessed January 2022]

WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization; 2018 https://www.who.int/publications/i/item/9789241550420 [Accessed November 2021]

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines